

PATENT SPECIFICATION

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NO DRAWINGS

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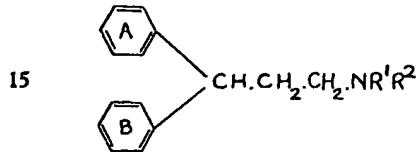
COMPLETE SPECIFICATION

Novel 3,3-Diphenylpropylamines and processes for the preparation thereof

We, ED. GEISTLICH SÖHNE AG FÜR CHEMISCHE INDUSTRIE, a body corporate organised and existing under the laws of Switzerland, of 6110, Wolhusen, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

10 This invention relates to new 3,3-diphenylpropylamine derivatives which have antidepressant activity.

According to the invention we provide alkane derivatives of the formula:—



wherein R¹ stands for hydrogen or an alkyl radical, and R² stands for an alkyl radical, and the phenyl radical A optionally bears one or two substituents selected from halogen atoms and the trifluoromethyl radical, and the phenyl radical B bears one or two substituents selected from halogen atoms and trifluoromethyl, alkyl and alkoxy radicals, and acid-addition salts thereof, provided that, when A stands for the phenyl radical and B stands for the 4-methylphenyl or 4-methoxyphenyl radical, R¹ and R² do not both stand for the methyl radical, and, when A stands for the phenyl radical and B stands for the 4-methylphenyl radical, R¹ and R² do not both stand for the ethyl radical.

As a suitable value for R², or for R¹ when it stands for an alkyl radical, there may be mentioned, for example, an alkyl radical of

not more than 6 carbon atoms and more particularly an alkyl radical of not more than 2 carbon atoms, for example the methyl radical.

The substituent(s) which may be present in the phenyl radical A may, for example, be selected from fluorine and chlorine atoms, and the trifluoromethyl radical. The substituent(s) which is or are present in the phenyl radical (B) may, for example, be selected from fluorine and chlorine atoms, the trifluoromethyl radical, and alkyl and alkoxy radicals of not more than 3 carbon atoms, for example the methyl and methoxy radical.

Preferred compounds of the invention are those wherein R¹ stands for hydrogen or the methyl radical, R² stands for the methyl or ethyl radical, and the phenyl radical A optionally bears one or two substituents selected from halogen atoms and the trifluoromethyl radical, and the phenyl radical B bears one or two substituents selected from halogen atoms and the trifluoromethyl radical.

As specific alkane derivatives of the invention there may be mentioned, by way of example, N,N-dimethyl-3,3-bis-(4-fluorophenyl)propylamine, N,N-dimethyl-3-(4-fluorophenyl)-3-phenylpropylamine, N,N-dimethyl-3-(4-chlorophenyl)-3-phenylpropylamine, N,N-dimethyl-3-(3-fluorophenyl)-3-phenylpropylamine, N,N-dimethyl-3-(2-methylphenyl)-3-phenylpropylamine, N,N-dimethyl-3-(2-methoxyphenyl)-3-phenylpropylamine, N,N-dimethyl-3-(3-fluorophenyl)-3-phenylpropylamine, N,N-dimethyl-3-(4-chlorophenyl)propylamine, N,N-dimethyl-3-(4-fluorophenyl)propylamine, N,N-dimethyl-3,3-bis-(3-fluorophenyl)propylamine, N,N-dimethyl-3,3-bis-(4-fluorophenyl)propylamine, N,N-dimethyl-3,3-bis-(3-fluorophenyl)propylamine and N,N-

[Price 4s. 6d.]

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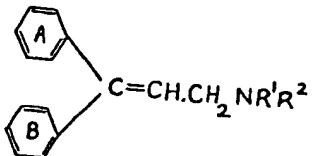
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dimethyl - 3 - (3 - trifluoromethylphenyl)-3 - phenylpropylamine, and acid-addition salts thereof.

5 As suitable acid-addition salts there may be mentioned salts derived from inorganic or organic acids affording pharmaceutically-acceptable anions, for example hydrochlorides, oxalates, citrates, maleates or tartrates.

10 According to a further feature of the invention we provide a process for the manufacture of the alkane derivatives of the invention, which comprises reducing an alkene derivative of the formula:—

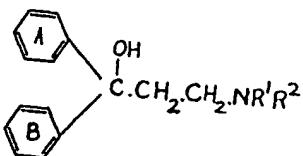


15 wherein A, B, R' and R'' have the meanings stated above, or an acid-addition salt thereof.

The reduction may be carried out, for example, by catalytic hydrogenation, for example by hydrogenation in the presence of a palladium-on-carbon catalyst.

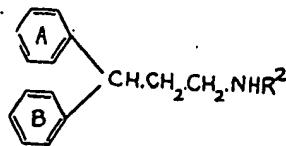
20 The hydrogenation may be carried out in an inert diluent or solvent, for example ethanol, and it may be carried out at ambient temperature or under the influence of heat, and at atmospheric or an elevated pressure. Alternatively, for example, the reduction may be carried out by the interaction of the alkene derivative with red phosphorus and hydriodic acid. In this case the alkene derivative may conveniently be formed *in situ* by interaction of the corresponding tertiary alcohol with red phosphorus and hydriodic acid.

25 The alkene derivatives used as starting materials in the above process (some of which are described and claimed in our co-pending Application No. 8165/66 (Serial No. 1134715) may be obtained by dehydrating the corresponding hydroxy compounds of the formula:—

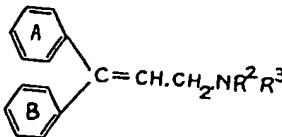


30 40 wherein A, B, R' and R'' have the meanings stated above, or an acid-addition salt thereof, by the interaction thereof with hydrochloric acid in the presence of a diluent or solvent, for example acetic acid.

45 According to a further feature of the invention we provide a process for the manufacture of those of the alkane derivatives of the invention which are of the formula:—



50 wherein A, B and R2 have the meanings stated above, and acid-addition salts thereof, which comprises hydrogenolysing a compound of the formula:—



55 wherein A, B and R2 have the meanings stated above, and R3 stands for a hydrogenolysable group, or an acid-addition salt thereof.

As a suitable value for R3 there may be mentioned, for example, the benzyl radical. The hydrogenolysis may be carried out by catalytic hydrogenation using the reactants and conditions described above.

60 The starting materials in the last-named process may be obtained by the general dehydration process outlined above.

65 The invention is illustrated but not limited by the following Examples in which the parts are by weight:—

EXAMPLE 1

5 Parts of N,N - dimethyl - 3,3 - bis - (4-fluorophenyl)prop-2 - enylamine hydrochloride are dissolved in 20 parts of dry ethanol. 2.5 Parts of 5% palladium-on-carbon catalyst are added, and the mixture is shaken in an atmosphere of hydrogen at ambient temperature and atmospheric pressure. When the absorption of hydrogen has ceased (approximately 10%, in excess of the calculated volume is absorbed), the catalyst is removed by filtration and the filtrate is evaporated to a small volume. Dry ether is slowly added until crystallisation begins, and 500 parts of dry ether are then added. The mixture is filtered and the solid residue is washed with dry ether and then dried. The solid is crystallised from ethyl acetate containing a trace of ethanol, and there is thus obtained N,N-dimethyl-3,3 - bis - (4 - fluorophenyl)propylamine hydrochloride, m.p. 188—189°C.

70 75 80 85 90 95 100 105 110 115 120 125 130 135 140 145 150 155 160 165 170 175 180 185 190 195 200 205 210 215 220 225 230 235 240 245 250 255 260 265 270 275 280 285 290 295 300 305 310 315 320 325 330 335 340 345 350 355 360 365 370 375 380 385 390 395 400 405 410 415 420 425 430 435 440 445 450 455 460 465 470 475 480 485 490 495 500 505 510 515 520 525 530 535 540 545 550 555 560 565 570 575 580 585 590 595 600 605 610 615 620 625 630 635 640 645 650 655 660 665 670 675 680 685 690 695 700 705 710 715 720 725 730 735 740 745 750 755 760 765 770 775 780 785 790 795 800 805 810 815 820 825 830 835 840 845 850 855 860 865 870 875 880 885 890 895 900 905 910 915 920 925 930 935 940 945 950 955 960 965 970 975 980 985 990 995 1000 1005 1010 1015 1020 1025 1030 1035 1040 1045 1050 1055 1060 1065 1070 1075 1080 1085 1090 1095 1100 1105 1110 1115 1120 1125 1130 1135 1140 1145 1150 1155 1160 1165 1170 1175 1180 1185 1190 1195 1200 1205 1210 1215 1220 1225 1230 1235 1240 1245 1250 1255 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2260 2265 2270 2275 2280 2285 2290 2295 2300 2305 2310 2315 2320 2325 2330 2335 2340 2345 2350 2355 2360 2365 2370 2375 2380 2385 2390 2395 2400 2405 2410 2415 2420 2425 2430 2435 2440 2445 2450 2455 2460 2465 2470 2475 2480 2485 2490 2495 2500 2505 2510 2515 2520 2525 2530 2535 2540 2545 2550 2555 2560 2565 2570 2575 2580 2585 2590 2595 2600 2605 2610 2615 2620 2625 2630 2635 2640 2645 2650 2655 2660 2665 2670 2675 2680 2685 2690 2695 2700 2705 2710 2715 2720 2725 2730 2735 2740 2745 2750 2755 2760 2765 2770 2775 2780 2785 2790 2795 2800 2805 2810 2815 2820 2825 2830 2835 2840 2845 2850 2855 2860 2865 2870 2875 2880 2885 2890 2895 2900 2905 2910 2915 2920 2925 2930 2935 2940 2945 2950 2955 2960 2965 2970 2975 2980 2985 2990 2995 3000 3005 3010 3015 3020 3025 3030 3035 3040 3045 3050 3055 3060 3065 3070 3075 3080 3085 3090 3095 3100 3105 3110 3115 3120 3125 3130 3135 3140 3145 3150 3155 3160 3165 3170 3175 3180 3185 3190 3195 3200 3205 3210 3215 3220 3225 3230 3235 3240 3245 3250 3255 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8260 8265 8270 8275 8280 8285 8290 8295 8300 8305 8310 8315 8320 8325 8330 8335 8340 8345 8350 8355 8360 8365 8370 8375 8380 8385 8390 8395 8400 8405 8410 8415 8420 8425 8430 8435 8440 8445 8450 8455 8460 8465 8470 8475 8480 8485 8490 8495 8500 8505 8510 8515 8520 8525 8530 8535 8540 8545 8550 8555 8560 8565 8570 8575 8580 8585 8590 8595 8600 8605 8610 8615 8620 8625 8630 8635 8640 8645 8650 8655 8660 8665 8670 8675 8680 8685 8690 8695 8700 8705 8710 8715 8720 8725 8730 8735 8740 8745 8750 8755 8760 8765 8770 8775 8780 8785 8790 8795 8800 8805 8810 8815 8820 8825 8830 8835 8840 8845 8850 8855 8860 8865 8870 8875 8880 8885 8890 8895 8900 8905 8910 8915 8920 8925 8930 8935 8940 8945 8950 8955 8960 8965 8970 8975 8980 8985 8990 8995 9000 9005 9010 9015 9020 9025 9030 9035 9040 9045 9050 9055 9060 9065 9070 9075 9080 9085 9090 9095 9100 9105 9110 9115 9120 9125 9130 9135 9140 9145 9150 9155 9160 9165 9170 9175 9180 9185 9190 9195 9200 9205 9210 9215 9220 9225 9230 9235 9240 9245 9250 9255 9260 9265 9270 9275 9280 9285 9290 9295 9300 9305 9310 9315 9320 9325 9330 9335 9340 9345 9350 9355 9360 9365 9370 9375 9380 9385 9390 9395 9400 9405 9410 9415 9420 9425 9430 9435 9440 9445 9450 9455 9460 9465 9470 9475 9480 9485 9490 9495 9500 9505 9510 9515 9520 9525 9530 9535 9540 9545 9550 9555 9560 9565 9570 9575 9580 9585 9590 9595 9600 9605 9610 9615 9620 9625 9630 9635 9640 9645 9650 9655 9660 9665 9670 9675 9680 9685 9690 9695 9700 9705 9710 9715 9720 9725 9730 9735 9740 9745 9750 9755 9760 9765 9770 9775

A	B	m.p. (°C.)	Crystallisation solvent(s)
Ph	4-F-Ph	141-144	n-butyl acetate
Ph	4-Cl-Ph	154-157	ethyl acetate—trace of ethanol
Ph	3-F-Ph	166-168	„
Ph	2-Me-Ph	165-167	„
Ph	2-MeO-Ph	166-167	„
Ph	3-CF ₃ -Ph	145-148	ethyl acetate—petroleum ether (b.p. 60-80°C.)
4-Cl-Ph	4-Cl-Ph	193-196	n-butyl acetate
4-Cl-Ph	4-F-Ph	173-176	n-butyl acetate
3-F-Ph	3-F-Ph	178-180	ethyl acetate—trace of ethanol
3-CF ₃ -Ph	3-CF ₃ -Ph	158-160	ethyl acetate—petroleum ether (b.p. 60-80°C.)

The N,N - dimethyl - 3,3 - bis-(4-fluorophenyl)prop - 2 - enylamine hydrochloride used as starting material in the process described above may be obtained as follows:—

A mixture of 6 parts of N,N - dimethyl - 3,3 - bis - (4 - fluorophenyl) - 3 - hydroxypropylamine (m.p. 120°C.), 50 parts of acetic acid and 15 parts of 10N-hydrochloric acid is heated at 100°C. for 3 hours. The reaction mixture is evaporated to small volume and the residual oil is dissolved in water. The solution is washed with ether and is then made 5 strongly alkaline by the addition of 2N-aqueous sodium hydroxide and is then extracted with ether. The ethereal extract is dried over anhydrous calcium sulphate and an ethereal solution of hydrogen chloride is then added to the extract until the precipitation of solid is complete. The precipitated solid is collected by filtration and is then crystallised from butyl acetate. There is thus obtained N,N - dimethyl - 3,3 - bis - (4 - fluorophenyl) - prop - 2 - enylamine, m.p. 209°C.

The N, N - dimethyl - 3,3 - bis - (4-fluorophenyl) - 3 - hydroxypropylamine used as starting material can be obtained in conventional manner by the interaction of the appropriate Grignard reagent with the appropriate ketone.

The alkene derivatives used as starting materials for the preparation of the alkane derivatives listed in the above table may be obtained in similar manner to that described for N,N - dimethyl - 3,3 - bis - (4 - fluorophenyl)prop - 2 - enylamine hydrochloride.

EXAMPLE 2

6 Parts of N - benzyl - N - methyl - 3,3 - bis - (4 - fluorophenyl) - prop - 2 - enylamine hydrochloride are dissolved in 30 parts of dry ethanol. 3 Parts of 5% palladium-on-carbon catalyst are added, and the mixture is shaken in an atmosphere of hydrogen at ambient temperature and atmospheric pressure. When the absorption of hydrogen has ceased (approximately 10% in excess of the calculated volume is absorbed), the catalyst is removed by filtration and the filtrate is evaporated. The residue is dissolved in 50 parts of water, and the solution is basified with ammonia. The base is extracted twice, each time with 100 parts of ether, and the combined ethereal extracts are dried with anhydrous magnesium sulphate. To the dry ethereal solution there is added an ethereal solution of oxalic acid until precipitation is complete. The mixture is filtered, and the solid residue is washed with ether and then dried on the filter. The solid is crystallised from ethanol, and there is thus obtained N - methyl - 3,3 - bis - (4 - fluorophenyl)propylamine oxalate, m.p. 187-190°C.

The N - benzyl - N - methyl - 3,3 - bis - (4 - fluorophenyl) - prop - 2 - enylamine hydrochloride used as starting material may be obtained as follows:—

A mixture of 58.3 parts of N - benzyl - N - methyl - 3,3 - bis - (4 - fluorophenyl) - 3 - hydroxypropylamine, 465 parts of acetic acid and 117 parts of 10N-hydrochloric acid is heated under reflux for 0.5 hour. The mixture is evaporated to small volume and the residual oil is dissolved in water. The solution

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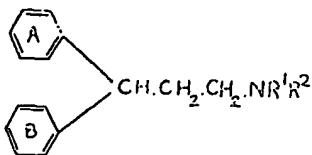
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is made strongly alkaline by the addition of 2N-aqueous sodium hydroxide and is then extracted with ether. The ethereal extract is dried over anhydrous calcium sulphate and is 5 evaporated *in vacuo*. The residual oil is fractionally distilled at a pressure of 0.2mm Hg. and the fraction having b.p. 172-178°C. is 10 collected. There is thus obtained N - benzyl - N - methyl - 3,3 - bis - (4 - fluorophenyl) - prop - 2 - enylamine, which may be converted into the hydrochloride (m.p. 132°C.) by conventional means.

N - Benzyl - N - methyl - 3,3 - bis - 15 (4 - fluorophenyl) - 3 - hydroxypropylamine can be obtained in conventional manner by the interaction of ethyl 3 - (N - benzyl - N - methylamino)propionic acid and the appropriate Grignard reagent.

WHAT WE CLAIM IS:—

20 1. An alkane derivative of the formula:—



25 wherein R¹ stands for hydrogen or an alkyl radical, and R² stands for an alkyl radical, and the phenyl radical A optionally bears one or two substituents selected from halogen atoms and the trifluoromethyl radical, and the phenyl radical B bears one or two substituents selected from halogen atoms and trifluoromethyl, alkyl and alkoxy radicals, or an acid-addition salt thereof, provided that, when A stands for the phenyl radical and B stands for the 4 - methylphenyl or 4 - methoxyphenyl radical, R¹ and R² do not both stand for the methyl radical, and, when A stands for the phenyl radical and B stands for the 4-methylphenyl radical, R¹ and R² do not both stand for the ethyl radical.

30 2. A compound as claimed in claim 1 wherein R¹ stands for hydrogen or an alkyl radical of not more than 6 carbon atoms, R² stands for an alkyl radical of not more than 6 carbon atoms, and the phenyl radical A optionally bears one or two substituents selected from fluorine and chlorine atoms and the trifluoromethyl radical, and the phenyl radical B bears one or two substituents selected from fluorine and chlorine atoms, the trifluoromethyl radical, and alkyl and alkoxy radicals of not more than 3 carbon atoms.

35 3. A compound as claimed in claim 1 wherein R¹ stands for hydrogen or the methyl radical, R² stands for the methyl or ethyl radical, the phenyl radical A optionally bears one or two substituents selected from halogen atoms and the trifluoromethyl radical, and the phenyl radical B bears one or two substituents

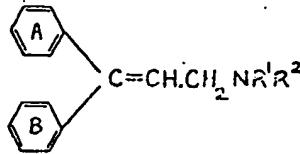
selected from halogen atoms and the trifluoromethyl radical.

4. A compound as claimed in claim 3 wherein the halogen substituent(s) present in 60 phenyl radical B, and optionally present in phenyl radical A, is or are selected from fluorine and chlorine atoms.

5. A compound selected from N,N - dimethyl - 3,3 - bis - (4 - fluorophenyl)propylamine, N,N - dimethyl - 3 - (4 - fluorophenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3 - (4 - chlorophenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3 - (3 - fluorophenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3 - (2-methylphenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3 - (2 - methoxyphenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3,3 - bis - (4 - chlorophenyl) - propylamine, N,N - dimethyl - 3 - (4-chlorophenyl) - 3 - (4 - fluorophenyl)propylamine, N,N - dimethyl - 3,3 - bis - (3-fluorophenyl) - propylamine, N - methyl - 3,3 - bis - (4 - fluorophenyl)propylamine, N,N - dimethyl - 3,3 - bis - (3 - trifluoromethylphenyl)propylamine and N,N - dimethyl - 3 - (3 - trifluoromethylphenyl) - 3 - phenylpropylamine, and acid-addition salts thereof.

6. An acid-addition salt as claimed in any of claims 1 to 5 which is a hydrochloride, 85 oxalate, citrate, maleate or tartrate.

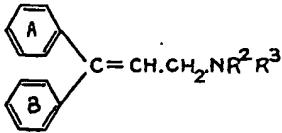
7. A process for the manufacture of a compound claimed in any of claims 1 to 6, which comprises reducing an alkene derivative of 90 the formula:—



wherein A, B, R¹ and R² have the meanings stated in claim 1, or an acid-addition salt thereof.

8. A process as claimed in claim 7 in which the reduction is carried out by hydrogenation in the presence of a palladium-on-carbon catalyst.

9. A process for the manufacture of a compound claimed in claim 1 wherein R¹ stands for hydrogen, which comprises hydrogenolysing a compound of the formula:—



wherein A, B and R² have the meanings stated above, and R³ stands for a hydro-

genolysable group, or an acid-addition salt thereof.

5 10. An alkane derivative, claimed in claim 1, substantially as described in either of the foregoing Examples.

11. A process for the manufacture of an

alkane derivative, claimed in claim 7 or 9, substantially as described in either of the foregoing Examples.

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